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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/253,573	02/19/99	CHEN H	99.001

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EXAMINER	
SCHNIZER,R	

ART UNIT	PAPER NUMBER
1632	3

DATE MAILED: 10/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

FILE COPY

Office Action Summary	Application No. 09/253,573	Applicant(s) Chen
	Examiner Richard Schnizer	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-43 is/are pending in the application.

Of the above, claim(s) 30-43 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-29 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-29, drawn to methods of gene therapy, classified in class 514, subclass 44.

II. Claims 30-43, drawn to proteins, classified in class 530, subclass 350.

The inventions are distinct, each from the other because of the following reasons:

The proteins of group II are related to the method of group I because expression of the proteins is required for practice of the method. However, these inventions are distinct because the proteins can be produced by other means, such as naturally or by chemical synthesis, and because the proteins can be used for purposes other than therapy, such as antibody production or functional investigations.

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification and their recognized divergent subject matter, and because each invention requires a separate, non-coextensive search, restriction for examination purposes as indicated is proper.

During telephone conversations with Yi Li on 6/15/99 a provisional election was made with traverse to prosecute the invention of group I, claims 1-29. Claims 30-43 have been

withdrawn from consideration by the examiner, and claims 1-29 are under consideration in this Office Action.

Claim Objections

Claims 13 and 27 are objected to because of the following informalities: These claims are ungrammatical. Specifically, the word "occurred" should be replaced by the word "occurring". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention is a method of delivering proteins in which red blood cells comprising the proteins are induced to rupture *in vivo*. The asserted utility of the invention is the therapy of a wide variety of diseases. Neither the prior art nor the specification discloses a method for

selectively lysing only red blood cells which comprise a protein of interest. Because the method is asserted to be therapeutic, it is assumed that general lysis of all red blood cells in an organism is not acceptable. A skilled artisan would be required to perform undue experimentation to perform therapy while simultaneously lysing the red blood cells of an organism.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivery of a protein to the blood *in vivo*, and to a cell expressing receptors for the protein, does not reasonably provide enablement for delivery of a protein to a cell which lacks receptors for the protein, nor does it provide enablement for therapy based on the delivery of any protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature of the invention. The invention is a method of delivering proteins *in vivo* by transfecting red blood cell precursors *ex vivo*, engrafting the transfected precursors, and allowing the production and ultimate lysis of red blood cells containing the protein of interest. The asserted utilities of the invention comprise therapies of a wide variety of diseases including muscular dystrophy, familial hypercholesterolemia, and Gaucher's disease, among others.

Breadth of the claims. The claims encompass treatment of diseases which arise from a deficiency of a cellular protein or a membrane protein, as well as from deficiencies of proteins

normally found in the blood. The scope of the diseases which can be treated with the invention is not limited by the specification.

State of the prior art. A review of the prior art shows that techniques for isolating, transfecting, and successfully engrafting red blood cell progenitor cells are established. However, obtaining sufficient expression of proteins for therapeutic purposes is problematic. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two recently published reviews. Verma et al (1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and **poor gene expression after genes are delivered**" (p.30).

Guidance and exemplification in the specification. The specification does not identify specific proteins which should be used to treat a variety of diseases such as Huntington's disease, Gaucher's disease or familial hypercholesterolemia. Assuming that one would treat familial hypercholesterolemia by administration of functional LDL-receptors, no guidance or exemplification is provided as to how these receptors could be induced to properly integrate into a cell membrane without the aid of a ribosome, and from the wrong side of the membrane.

Further, the specification does not teach what dosage or course of administration of any protein is desirable for the treatment of any disease, nor does it teach how many cells should be transfected for any given treatment, or how to protect the released proteins from the proteases present in blood.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In this case Applicant proposes gene therapy of several diseases for which there is currently no successful treatment and for which no guidance or exemplification is provided. Because there are no proven examples of successful gene therapy, and in light of the lack of guidance and exemplification, the probability of success in gene therapy using the instant invention is extremely low.

Amount of experimentation necessary. A skilled artisan would be required to perform extensive experimentation in order to develop gene therapy protocols for the variety of diseases recited in the specification. There is no currently successful gene therapy protocols for any disease, and there is no teaching or exemplification in the specification to guide the artisan.

Due to the lack of guidance in the specification with respect to nucleotide dosages, quantities of cells which should be transfected, and the preferred level and temporal profile of expression for treatment of each disease; due to the general expectation that it will require years of further research to develop effective nucleic acid-based therapies; and due to the unpredictable nature of the art, a skilled artisan would be required to perform undue experimentation in order to develop successful gene therapy protocols utilizing the instant invention.

In further consideration of claims 1-29, the specification, while being enabling for expression of a gene which is operatively linked to a promoter, does not reasonably provide enablement for the expression of a gene which is not operably linked to a promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention is a method of expressing genes in a cell. The claims encompass genes in vectors which comprise a promoter. The claims do not limit the relationship between the promoter and the gene. The prior art indicates that transcription of a gene is dependent on operative linkage to an expression control sequence such as a promoter or enhancer. A skilled artisan would be required to perform undue experimentation do achieve gene expression in the absence of such operable linkage.

It is suggested that the claims be amended to recite operable linkage between an expression control sequences and the gene.

With respect to claims 1-15, the specification, while being enabling for expression of a gene which is operatively linked to a promoter which is active in red blood cell precursors, does not reasonably provide enablement for the expression of a gene which is not operably linked to a promoter which is not active in red blood cell precursors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention is a method of expressing a protein in red blood cell precursors. The claims encompass a wide variety of promoter/gene combinations. Claim 5, which recites the narrowest limitation on the identity of the promoter, allows the use of any non-hemoglobin promoter native to red blood cells. Mammalian red blood cells which retain nuclei comprise 60,000 to 100,000 genes, each of which has a promoter which is native to the red blood cell. Most of these promoters are not functional in a red blood cell. A skilled artisan would be required to perform undue experimentation to achieve gene expression in a red blood cell, or its precursor, using a promoter which was not active in that cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5-9, 11, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Schlegel (US Patent 5,576,206, issued 11/19/96) .

Schlegel teaches a method of obtaining red blood cell progenitors from an individual, transfecting them with a retroviral or adenoviral vector comprising a gene of interest under the control of an actin promoter, and reintroducing the cells into the individual. The gene of interest may be an enzyme (Factor IX), a cofactor (Factor VIII), an interferon, or a hormone. See column

3, lines 22-36; column 5, lines 10, 26, and 62-64; column 7 lines 6-15; column 9, lines 10, 34, 40, and 44-47. Schlegel does not teach that the red blood cells should lyse and release the protein into the blood. However, lysis of red blood cells is an inherent property, therefore Schlegel anticipates the claims.

It is noted that while the disclosure of Schlegel is enabling for the expression of proteins *in vivo*, it is not enabling for gene therapy.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 7, 11-23, and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlegel (US Patent 5,576,206, issued 11/19/96), Carrano (US Patent 5,739,118, issued 4/14/98), Wickham et al (US Patent 5,846,782, issued 12/8/98, Rixon et al (Mol. Cell. Biol. 8(2): 713-721, 1988), Zhang et al (Shengwu Huaxue Zazhi 11(3): 343-347, 1995), and Chatterjee et al (US Patent 5935821, filed 11/21/96).

The invention is a method of producing and delivering a protein *in vivo*. The protein is produced by transfecting red blood cell precursors with an expression vector *ex vivo*, engrafting the transfected cells, allowing them to express the protein as they differentiate into red blood cells,

and allowing the red blood cells to eventually lyse, releasing the protein into the blood. The vector may comprise an enhancer, a hemoglobin promoter, a mutated promoter, or a mutated hemoglobin promoter, and it may be delivered by a lentiviral vector.

Schlegel teaches a method of obtaining red blood cell progenitors from an individual, transfecting them with a retroviral or adenoviral vector comprising a gene of interest under the control of an actin promoter, and reintroducing the cells into the individual. The gene of interest may be an enzyme (Factor IX), a cofactor (Factor VIII), an interferon, or a hormone. See column 3, lines 22-36; column 5, lines 10, 26, and 62-64; column 7 lines 6-15; column 9, lines 10, 34, 40, and 44-47. Schlegel does not teach the use of an enhancer, a hemoglobin promoter, any mutated promoter, or a lentiviral vector. Neither does Schlegel teach the expression of a peptide, an antibody, a fusion protein, or a mutated protein.

Carrano teaches a method of isolating cells from an individual, delivering expression vectors to the cells *ex vivo*, and reimplanting the cells. The expression vector may utilize a hemoglobin promoter, and an enhancer. The protein may be a fusion protein (gag/pol) or a mutated protein (either env or gag/pol expressed separately from each other). See column 1, lines 52-67; column 12, lines 63-67, column 22, lines 32-37; column 5, line 26, column 23, lines 41 and 42; column 24, lines 28-32.

Wickham teaches that lentiviruses are useful for gene transfer to hematopoietic cells. See column 11, lines 52-55; column 12, lines 29-31, and 41-44; and column 19, lines 14-18.

Rixon teaches a mutated hemoglobin promoter having increased activity relative to the wild type. See entire abstract, particularly the third and last sentences.

Zhang suggests the transfer of an expression cassette, comprising the promoter of Rixon, into hematopoeitic stem cells. See last sentence of abstract.

Chatterjee teaches genetic immunization by delivery and expression of nucleic acids encoding an antibody, or peptides or fusion proteins thereof. See column 4, lines 59-64; and column 23, lines 25-30; column 24, lines 5-9.

It would have been obvious to one of ordinary skill in the art at the time of the invention to utilize an enhancer, a hemoglobin promoter, or a mutated hemoglobin promoter in the invention of Schlegel. One would have been motivated to use an enhancer or a hemoglobin promoter, because Carrano teaches that vectors comprising these elements can be used to express proteins in cells transfected *ex vivo* and reimplanted into the host. Further, one of ordinary skill in the art appreciates that enhancers increase the expression of genes, and that hemoglobin promoters are active in the red blood cell progenitors taught by Schlegel. One would have been motivated to use a mutated hemoglobin promoter, because Rixon teaches a mutated hemoglobin promoter with enhanced transcriptional activity, and Zhang suggests the use of this promoter to drive expression of proteins in hematopoietic stem cells.

It would have been similarly obvious to deliver the expression cassette to the cells using a lentiviral vector. One would have been motivated to do so because Wickham demonstrates that lentiviral vectors are useful for gene transfer to hematopoietic cells.

Finally it would have been obvious to use the system of Schlegel to express an antibody, a fusion protein, a peptide, or a mutated protein. In this respect, a peptide or a truncated portion of a protein can be viewed as a mutated protein. One would have been motivated to do so because Chatterjee teaches a method of genetic immunization in which polynucleotides encoding either an antibody, fusion proteins comprising the antibody, or pentapeptides derived from the antibody are expressed in an individual. Also Chatterjee teaches that the polynucleotides may be delivered to peripheral blood cells for ongoing secretion of the protein of interest. The method of Schlegel would facilitate such extended expression.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Claims 10 and 24 appear to be free of the art.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800